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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,192	03/11/2004	Richard O. Snyder	5853-258-1CON	5141

7590 11/15/2005

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EXAMINER	
GUZO, DAVID	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,192	SNYDER ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Applicants' submission of a Petition to Revive the abandoned parent application 10/456,423 is acknowledged. However, since no decision on the Petition has been made by the Office of Petitions at the time of this Office Action, the chain of continuity between the '423 application and this instant application remains broken and applicants are not entitled to benefit of the 10/456,423 application or the 60/385,864 provisional application.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have amended Claim 1 to recite that the third nucleotide sequence encodes a transcription product having at least one Adenoviral helper function in reverse orientation to the first and second AAV nucleotide sequences. Applicants point to Figure 1 and Example 1 on pages 17-18 for support for the newly added subject matter. As far as can be determined from Fig. 1 and the specification, it appears that

applicants have generated two vectors (pXYZ1 and pXYZ5) which have one specific adenoviral helper sequence (the adenoviral VA nucleotide sequence) in reverse orientation to the first two AAV sequences while other adenoviral helper sequences (i.e. E4) are in the same orientation as the first two AAV sequences. The scope of the amended claims is broader than (generic to) the instant disclosure in that the claims read on a nucleic acid molecule comprising at least one (reading on one **or more**) adenoviral helper functions in reverse orientation to the first and second AAV sequences wherein the specification only supports specific plasmids **containing only the adenovirus sequence encoding the VA helper function in reverse orientation**. This is a NEW MATTER rejection.

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 20-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Gao et al.

This rejection is maintained for reasons of record in the previous Office Action (Mailed 3/25/05) and for reasons outlined below. The rejection is expanded to include claims 29-32 as a result of applicants' amendment filed 9/29/05.

Applicants responded to this rejection by amending claim 1 to differentiate it from the teachings of Gao et al. and indicate that the rejection no longer applies to claims 1-28 as a result of the amendment.

Applicant's arguments filed 9/29/05 have been fully considered but they are not persuasive. Claims 20-28 have not been amended to recite the limitations in amended claim 1 and indeed, claims 20-28 read on the same nucleic acid molecule (and cell containing said nucleic acid) as originally claimed in claim 1 and previously rejected over Gao et al. in the previous Office Action.

With regard to claims 29-32, Gao et al. (see Gao et al. (US 2005/0014262, published 01/20/2005, priority to 12/17/2001, see whole document, particularly paragraphs [0040]-[0052]; [0057]-[0063]; [0066]; [0069]; [0073]: [0076]; [0080]-[0084]: [0121]; [0124]; [0044], [0129]) teaches the claimed methods of producing rAAV virions wherein mammalian cells (i.e. 293 cells) comprising the recited AAV and adenoviral helper nucleic acids are cultured so as to produce rAAV virions, the cells are separated from the medium, lysed and the rAAV virions are isolated from the lysate. Gao et al. therefore teaches the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 20-27 and 29-33 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Fraites et al.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below. The rejection is expanded to include claims 28-33 as a result of applicants' amendment filed 9/25/05.

Applicants responded to this rejection by amending Claim 1 as recited above. Applicants also argue that the limitations newly added to Claim 1 render the invention distinct from that recited by Fraites et al. and that Fraites et al. does not teach the selection of different serotype combinations nor how to generate AAV that are purified based upon their serotypes.

Applicant's arguments have been fully considered but they are not persuasive. Claims 20-27 have not been amended to recite the limitations in amended claim 1 and indeed, claims 20-27 read on the same nucleic acid molecule (and cell containing said nucleic acid) as originally claimed in claim 1 and previously rejected over Fraites et al. in the previous Office Action. With regard to Claims 29-33, Fraites et al. (See Fraites et al. paragraphs Fig. 6; [0096]-[0097], [0102], [0019]-[0020], [0043]- [0046], [0062]-[0064], [0097]) teaches vector pXYZ1 which comprises sequences encoding the rep genes (rep52 and rep78) from AAV2 and the cap gene (VPI-VP3) from AAV1 as well as the adenoviral helper genes required for production of rAAV virions wherein the rep genes are under control of the p5 and p19 promoters and the cap gene is under control of the

p40 promoter. The vector backbone for pXYZ1 contains sequences encoding ampicillin resistance as a selectable marker. Fraites et al. also teaches that the rAAVs can comprise a cap sequence from any serotype such as AAV5, mammalian cells containing the vector as well as AAV2 vectors (i.e. AAV ITRs) comprising a transgene to be expressed wherein the transgene can be a marker. Fraites also teaches the recited method for producing rAAV virions comprising culturing the mammalian cells containing the pXYZ1 vector, lysing the cells and isolating the virions from the lysates through use of iodixanol gradients. Fraites et al. therefore teaches the claimed invention.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

35 USC 103(a) Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. in view of Rabinowitz et al.

Applicants claim a method for isolating rAAV virions comprising the steps of subjecting the rAAV virions produced to an iodixanol step gradients and ion exchange chromatography and wherein the rAAV have a serotype 1 or 5 capsid.

Gao et al. is recited as in the above 35 USC 102(e) rejection. Gao et al. does not teach use of iodixanol step gradients and ion exchange chromatography to purify rAAV virions.

Gao et al. teaches the claimed invention with the exception of the purification methods for the rAAV vectors produced by the producer cells.

Rabinowitz et al. (US 6,491,907, issued 12/10/02, filed 11/10/1999, see whole document, particularly columns 25 and 39) teaches that rAAV virions can be purified by iodixanol step gradient purification and/or ion exchange chromatography.

The ordinary skilled artisan, seeking to purify the rAAV vectors generated by Gao et al. would have been motivated to use iodixanol step gradients to purify rAAV virions because Rabinowitz et al. teaches that iodixanol gradients are less harsh that CsCl

gradients and have been shown to result in increased virus recovery. The ordinary skilled artisan would have subsequently been motivated to use ion exchange chromatography to purify the rAAV virions because Rabinowitz et al. indicates that known techniques to purify rAAV virions such as ion exchange chromatography can also be used. The ordinary skilled artisan would have been motivated to use both iodixanol step gradient purification followed by purification by ion exchange chromatography to achieve the high levels of purity of the rAAV virion compositions which are required for *in vivo* use in human gene therapy procedures. It would have been obvious for the ordinary skilled artisan to do this because iodixanol step gradients and ion exchange chromatography are standard methods for purifying rAAV virions, as recited by Rabinowitz et al. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

35 USC 112, 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims 2-19) are vague in that applicants recite a nucleotide sequence encoding a AAV cap protein "generated by SEQ ID NO's:1-4". It appears that SEQ ID NO's:1-4 are primers and it is unclear how cap protein encoding sequence can be "generated" from these primers. If applicants mean to recite use of primers to amplify cap encoding sequences by PCR or related methods, they should claim this.

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
November 3, 2005

DAVID GUZO
PRIMARY EXAMINER